The tobacco industry contends that tobacco is used for pleasure. So, too, is cocaine used for pleasure. These data establish, however, that receiving nicotine through a route that does not provide any sensory qualities of tobacco use (e.g., through the venous system) also is pleasurable. Thus, the pharmacological effects of nicotine administered through non-inhalation routes are able to produce the characteristic psychoactive effects of tobacco use.

Self-administration testing. In self-administration testing, human or animal subjects are given access to a drug and then evaluated for their tendency to seek repeated doses of the drug. The self-administration test determines the ability of a drug to sustain drug-seeking behavior—one of the key distinguishing features of drug dependence. The self-administration test is widely used to determine whether a drug can control behavior; a drug whose intake leads to more consumption is called a "positive reinforcer." It is generally accepted in the scientific community that the ability of addictive drugs to serve as positive reinforcers is the core property that promotes the development and maintenance of addiction.[86]

Self-administration procedures using primates and rats have been shown to be valid and reliable predictors of the potential for a compound to result in drug dependence. There is a strong correlation between the types of drugs that serve as reinforcers in animals and the drugs associated with addiction in humans.[87]

Henningfield JE, Miyasato K, Jasinski DR, Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine, *Journal of Pharmacology and Experimental Therapeutics*, 1985;234(1):1-12. *See* AR (Vol. 39 Ref. 69).

[86] Balster RL, Drug abuse potential evaluation in animals, *British Journal of Addiction* 1991;86:1549-1558. *See* AR (Vol. 8 Ref. 89).

[87] Griffiths RR, Bigelow GE, Henningfield JE, Similarities in animal and human drug-taking behavior, *Advances in Substance Abuse* 1980;1:1-90. *See* AR (Vol. 8 Ref. 91-2).

Animal self-administration studies, using a variety of administration schedules and controls, have shown that nicotine functions as a positive reinforcer across several species.[88] Nicotine is more avidly self-administered when available on an intermittent schedule than when freely available.[89] Since tobacco users self-administer intermittent doses of nicotine per cigarette or pinch of smokeless tobacco, the schedule of nicotine administration that is most reinforcing in animals corresponds to the pattern of actual tobacco consumption.

Consistent with animal self-administration studies, analogous studies with humans in the 1980's demonstrated that nicotine serves as a positive reinforcer under controlled laboratory conditions.[90] Subjects self-administered intravenous nicotine in a regular and

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Woolverton WL, Nader MA, Experimental evaluation of the reinforcing effects of drugs, in *Modern Methods in Pharmacology*, eds. Adler MW, Cowen A (New York: Wiley-Liss, 1990), 6:165-192. *See* AR (Vol. 535 Ref. 96, vol. III.N).

[88] Goldberg SR, Spealman RD, Goldberg DM, Persistent behavior at high rates maintained by intravenous self-administration of nicotine, *Science* 1981;214:573-575. *See* AR (Vol. 5 Ref. 35-2).

Goldberg SR, Spealman RD, Maintenance and suppression of behavior by intravenous nicotine injections in squirrel monkeys, *Federation Proceedings* 1982;41(2):216-220. *See* AR (Vol. 39 Ref. 52).

Spealman RD, Goldberg SR, Maintenance of scheduled-controlled behavior by intravenous injections of nicotine in squirrel monkeys, *Journal of Pharmacology and Experimental Therapeutics* 1982;223(2):402-408. *See* AR (Vol. 42 Ref. 146).

Risner ME, Goldberg SR, A comparison of nicotine and cocaine self-administration in the dog: fixed-ratio and progressive-ratio schedules of intravenous drug infusion, *Journal of Pharmacology and Experimental Therapeutics* 1983;224(2):319-326. *See* AR (Vol. 42 Ref. 119).

Cox BM, Goldstein A, Nelson WT, Nicotine self-administration in rats, *British Journal of Pharmacology* 1984;83:49-55. *See* AR (Vol. 8 Ref. 93-1).

Slifer BL, Balster RL, Intravenous self-administration of nicotine: with and without schedule-induction, *Pharmacology, Biochemistry and Behavior* 1985;22:61-69. *See* AR (Vol. 8 Ref. 93-3).

Corrigall WA, Coen KM, Nicotine maintains robust self-administration in rats on a limited access schedule, *Psychopharmacology* 1989;99:473-478. *See* AR (Vol. 347 Ref. 5495).

[89] Surgeon General's Report, 1988, at 182-189. *See* AR (Vol. 129 Ref. 1592).

[90] Henningfield JE, Miyasoto K, Jasinski DR, Cigarette smokers self-administer intravenous nicotine, *Pharmacology, Biochemistry and Behavior* 1983;19:887-890. *See* AR (Vol. 8 Ref. 97).

orderly pattern, giving themselves amounts of nicotine comparable to those they were accustomed to receiving from their cigarettes. These studies demonstrate that the pharmacological effects of nicotine can explain why people engage in compulsive consumption of tobacco.

At a molecular level, nicotine's reinforcing effects are widely believed to be a consequence of its actions on specific areas in the central nervous system. Within the scientific community, a consensus has emerged that nicotine, like other addictive drugs such as cocaine, amphetamine, and morphine, causes addiction by increasing the activity of the neurotransmitter dopamine within the mesolimbic system of the brain.[91] A very recent study, which expands on and confirms earlier studies, has demonstrated that nicotine, at doses known to be self-administered, mimics the effects of cocaine, morphine, and amphetamines in the mesolimbic system, by selectively increasing dopamine transmission and energy metabolism in a specific region of the nucleus accumbens previously shown to be important in mediating the addictive effects of these drugs.[92]

Surgeon General's Report, 1988, at 192. *See* AR (Vol. 129 Ref. 1592).

[91] Clarke PBS, Mesolimbic dopamine activation—the key to nicotine reinforcement? *CIBA Foundation Symposium* 1990;152:153-168. *See* AR (Vol. 3 Ref. 19-2).

Corrigall WA, Coen KM, Selective dopamine antagonists reduce nicotine self-administration, *Psychopharmacology* 1991;104:171-176. *See* AR (Vol. 66 Ref. 30).

Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

Iverson LL, . . . harmful to the brain, *Nature* 1996;382:206-207. *See* AR (Vol. 711 Ref. 51).

[92] Pontieri FE, Tanda G, Orzi F, *et al.*, Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs, *Nature* 1996;382:255-257. *See* AR (Vol. 711 Ref. 51).

Observing that food, water, and salt also increase dopamine activity in the mesolimbic system, the tobacco industry comments that nicotine's action is not unique. FDA's finding, however, is not that nicotine's role in this system is unique, but that it is *significant*. Indeed, the tobacco industry's own observation on food, water, and salt reflects the significance of nicotine's action. As researchers have noted, the mesolimbic "reward" system of the brain naturally reinforces the intake of essential substances (such as food, water, and salt) because these substances are necessary for human existence. Without an intrinsic reward for eating and drinking, humans would perish. Researchers believe that addictive substances such as nicotine, amphetamine, cocaine, and morphine are so powerful precisely because they activate and even control this natural system of reward. Indeed, the same scientists quoted by the tobacco industry state that "nicotine could substitute for food or other reinforcers" in the mesolimbic system.[93] That nicotine can mimic life-sustaining substances and alter such a pivotal neurological system demonstrates its substantial effect on the structure and function of the human body.

Withdrawal and tolerance. Documentation of a drug withdrawal syndrome is the primary method of establishing that a substance causes physical dependence. According to the Surgeon General, "[m]easurement of drug withdrawal phenomena entails recording physiological, subjective, and behavioral responses that occur when drug administration is terminated."[94] Numerous studies document a characteristic withdrawal syndrome,

[93] Mifsud JC, Hernandez L, Hoebel BG, Nicotine infused into the nucleus accumbens increases synaptic dopamine as measured by in vivo microdialysis, *Brain Research* 1989;478(2):365-367, at 367. *See* AR (Vol. 535 Ref. 96, vol. IILJ).

[94] Surgeon General's Report, 1988, at 291. *See* AR (Vol. 129 Ref. 1592).

including both physiological and psychological symptoms, associated with nicotine abstinence.[95] Widely used criteria for diagnosing withdrawal come from the American Psychiatric Association's DSM-IV, which defines Nicotine Withdrawal Syndrome as four (or more) of the following symptoms within 24 hours after cessation of use: dysphoric or depressed mood; insomnia; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain.[96] Although nicotine withdrawal is not as life-threatening as withdrawal from alcohol or some barbiturates, it is comparable to or stronger than withdrawal from such other stimulants as cocaine and can be highly disruptive to personal life.[97] After several weeks of nicotine exposure, users who are deprived of nicotine for more than a few hours can develop withdrawal symptoms.[98] Withdrawal symptoms after quitting tobacco use can persist for months.[99]

The tobacco industry contends that nicotine withdrawal is associated only with psychological changes; the evidence, however, demonstrates that tobacco abstinence also causes significant physiological effects on the body. These effects include decreased heart

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[95] *Id.* at 197-207.

[96] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

[97] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[98] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 548. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[99] Ryan FJ, Cold turkey in Greenfield, Iowa: a follow-up study, in *Smoking Behavior: Motives and Incentives*, ed. Dunn WL (Washington DC: VH Winston & Sons, 1973), at 231-234. *See* AR (Vol. 8 Ref. 105).

rate at rest and after standing, alteration of the electroencephalogram (EEG, a measure of brain electrical activity), skin temperature changes, and disruptions in sleep patterns.[100] Studies have also demonstrated that tobacco withdrawal can cause an increase in weight. This weight increase may be attributed to increased caloric intake, decreased metabolism, and decreased energy expenditure during nicotine withdrawal.[101] The physiological signs of nicotine withdrawal are substantially reversed when nicotine is given in a form other than tobacco.[102]

Significant behavioral and subjective symptoms common to nicotine withdrawal include depression, anger, irritability, anxiety, poor concentration, and restlessness.[103]

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[100] West RJ, Jarvis MJ, Russell MAH, *et al.*, Effect of nicotine replacement on the cigarette withdrawal syndrome, *British Journal of Addiction* 1984;79(2):215-219. *See* AR (Vol. 8 Ref. 102-1).

Hughes JR, Hatsukami D, Signs and symptoms of tobacco withdrawal, *Archives of General Psychiatry* 1986;43:289-294. *See* AR (Vol. 8 Ref. 102-2).

Hughes JR, Higgins ST, Hatsukami D, Effects of abstinence from tobacco: a critical review, *Research Advances in Alcohol and Drug Problems* 1990;10:317-398, at 382. *See* AR (Vol 535 Ref. 96, vol. III.G).

[101] Wack JT, Rodin J, Smoking and its effect on body weight and the systems of caloric regulations, *American Journal of Clinical Nutrition* 1982;35(2):366-380. *See* AR (Vol. 8 Ref. 103-1).

Glauser SC, Glauser EM, Reidenberg MM, *et al.*, Metabolic changes associated with the cessation of cigarette smoking, *Archives of Environmental Health* 1970;20:377-381. *See* AR (Vol. 8 Ref. 103-2).

[102] Surgeon General's Report, 1988, at 208. *See* AR (Vol. 129 Ref. 1592).

[103] *See, e.g.*, Hughes JR, Hatsukami D, Signs and symptoms of tobacco withdrawal, *Archives of General Psychiatry* 1986;43:289-294. *See* AR (Vol. 8 Ref. 102-2).

Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescent and young adult tobacco users-United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 7 Ref. 86).

Hughes JR, Nicotine withdrawal, dependence, and abuse, in *DSM-IV Sourcebook*, eds. Widiger T, Frances A, *et al.* (Washington DC: American Psychiatric Association, 1994), 1:109-116. *See* AR (Vol. 535 Ref. 96, vol. III.F).

West RJ, Jarvis MJ, Russell MAH, *et al.*, Effect of nicotine replacement on the cigarette withdrawal syndrome, *British Journal of Addiction* 1984;79(2):215-219. *See* AR (Vol. 8 Ref. 102-1).

Dependent smokers also show substantial withdrawal symptoms within a day of nicotine abstinence.[104] These psychological symptoms are substantially reversible or preventable by providing nicotine in the form of conventional cigarettes or by providing equivalent or lower doses of nicotine in other forms (e.g., nicotine gum) including forms without the taste of nicotine (e.g., nicotine patches).[105]

Withdrawal from smokeless tobacco also causes physiological changes attributable to nicotine abstinence. Hatsukami and colleagues showed the following changes in users deprived of chewing tobacco: (1) decreased heart rate at rest and after standing; (2) increased craving for tobacco; (3) increased confusion score on the Profile of Mood States (POMS) (this measures tension/anxiety, depression/dejection, confusion, anger/hostility, vigor, and fatigue); (4) increased eating; (5) increased number of sleep interruptions; and (6) increased total scores on a withdrawal symptom checklist for both self-rated and observer-rated measures.[106]

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[104] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 548. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[105] Surgeon General's Report, 1988, at 470-485. *See* AR (Vol. 129 Ref. 1592).

Robinson JH, Pritchard WS, Davis RA, Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine, *Psychopharmacology* 1992;108:466-472. *See* AR (Vol. 59 Ref. 236).

Fagerstrom KO, Sawe U, Tonnesen P, Therapeutic use of nicotine patches: efficacy and safety, *Journal of Drug Development* 1993;5:191-205. *See* AR (Vol. 76 Ref. 156).

Fiore MC, Jorenby DE, Baker TB, *et al.*, Tobacco dependence and the nicotine patch, *Journal of the American Medical Association* 1992;268:2687-2694. *See* AR (Vol. 351 Ref. 5609).

[106] Hatsukami DK, Gust SW, Keenan RM, Physiologic and subjective changes from smokeless tobacco withdrawal, *Clinical Pharmacology and Therapeutics* 1987;41:103-107. *See* AR (Vol. 7 Ref. 73).

A second key test of a substance's ability to produce physical dependence is whether it promotes tolerance.[107] Tolerance occurs when responses produced by an initial dose are diminished with repeated doses, so that increasing doses are necessary to reproduce the initial effects. Tolerance to some effects of a substance can be acute, occurring within hours to days, while tolerance to other effects develops chronically as a result of long-term substance exposure.

Tobacco users become tolerant to nicotine both acutely and chronically.[108] After a single night of abstinence, the nervous system[109] and the cardiovascular system[110] are highly responsive to small doses of nicotine. But after the administration of the equivalent of a few cigarettes, the responsiveness of the human body to nicotine declines markedly. Thus, a cigarette smoked in the middle of the day may not elicit the same psychological or physiological response in a cigarette smoker as one smoked earlier in the morning. This severe degree of acute tolerance seems to greatly exceed that produced by cocaine and to be more comparable to that produced by morphine.[111]

Tolerance to other effects of nicotine develops over weeks and months. For example, new smokers often experience nicotine-related effects such as dizziness, nausea, intoxication, vomiting, and headaches—symptoms that disappear eventually as the

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[107] Surgeon General's Report, 1988, at 50-54. *See* AR (Vol. 129 Ref. 1592).

[108] Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

[109] *Id.*

[110] Surgeon General's Report, 1988, at 47-48. *See* AR (Vol. 129 Ref. 1592).

[111] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522–573), at 533, 543, 548. *See* AR (Vol. 535 Ref. 96, vol. III.G).

smokers' bodies adapt to nicotine and tolerance to these effects develops.[112] These and other examples of chronic tolerance (such as faster nicotine metabolism among experienced smokers) are consistent with laboratory evidence of long-term structural changes in the brain and other parts of the body from nicotine use.[113]

There is also epidemiological evidence that the vast majority of smokers and smokeless tobacco users increase their consumption and usage of tobacco products over time. *See* section II.A.3.c.ii., below. This escalation of dose is an additional demonstration of the development of tolerance. Like users of other addictive drugs, tobacco users eventually reach a stable level of consumption.[114]

Laboratory studies on drug discrimination, psychoactive/subjective effects, self-administration, and withdrawal and tolerance thus demonstrate that nicotine has the properties of an addictive drug.

Nicotine compared to saccharin and caffeine. In its comments, the tobacco industry attempts to discount a multitude of laboratory studies of nicotine by selectively pointing to a single test used to screen for addictive substances and arguing that, in that test, nicotine's effect was similar to saccharin's. From this premise, the industry concludes that nicotine is no more addictive than saccharin. This argument misrepresents the published data on saccharin's and nicotine's properties and overlooks fundamental

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[112] Department of Health and Human Services, Office on Smoking and Health, *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Washington DC: Government Printing Office, 1994), at 138. *See* AR (Vol. 133 Ref. 1596).

[113] *See* section II.A.3.i. and ii., below, for a more detailed discussion.

[114] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-532). *See* AR (Vol. 535 Ref. 96, vol. III.G).

differences between saccharin and nicotine. Contrary to the tobacco industry's argument, saccharin has not been shown to meet the most fundamental test of an addictive drug, namely, psychoactive effects in the brain that account for its appeal to humans and animals. Nicotine *has* been shown to have these effects.

In contrast to nicotine, which can be pleasurable even when injected intravenously, saccharin is liked primarily because of its taste. For example, rats can be trained to self-administer oral doses of saccharin in preference to water, demonstrating only that rats prefer the taste of saccharin to that of water. FDA is unaware of any studies, and the tobacco industry cites none, in which rats have self-administered saccharin intravenously. Such a study would be an essential step in proving that saccharin's appeal lies in its effects on the brain. Moreover, there is no evidence that saccharin produces any psychoactive effects. In contrast, nicotine, which produces no such pleasant taste, demonstrates all of the properties of an addictive drug, including self-administration and psychoactivity, through its actions on the central nervous system.

The tobacco industry also argues that nicotine is similar to caffeine in tests of addictive potential. FDA disagrees. In comparison to the more orderly pattern of self-administration observed with nicotine and stimulant drugs, the pattern of caffeine self-administration is generally weak and sporadic in animals.[115] Hence, in comparison to known

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[115] Heishman SJ, Henningfield JE, Stimulus functions of caffeine in humans: relation to dependence potential, *Neuroscience and Biobehavioral Reviews* 1992;16:273-287. *See* AR (Vol. 79 Ref. 230).

Griffiths RR, Woodson PP, Reinforcing properties of caffeine: studies in humans and laboratory animals, *Pharmacology, Biochemistry and Behavior* 1988;29(2):419-427. *See* AR (Vol. 535 Ref. 96, vol. III.E).

Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522–573), at 524. *See* AR (Vol. 535 Ref. 96, vol. III.G).